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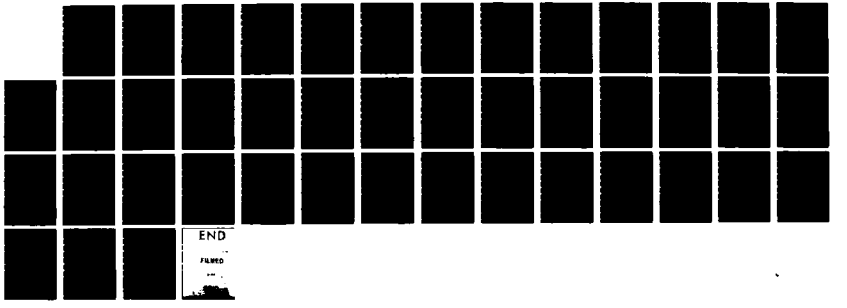

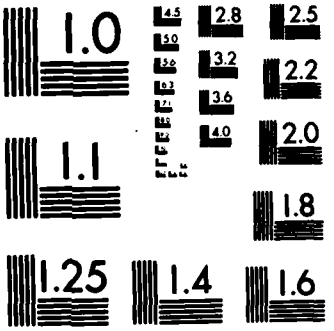

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The regulation and patterns of cold-induced vasodilation (CIVD) were identified by simultaneously monitoring circulatory and thermal responses during local cold exposure of a hindlimb in 22 cats anesthetized with chloralose. The different patterns of CIVD were categorized as hunting, sustained, combination of hunting and sustained, or no CIVD. The different regulatory mechanisms mediating CIVD were classified as baroreceptor mediated, active vasodilation, or redistribution of blood flow to skin. These cold unacclimatized cats produced primarily a hunting pattern of CIVD which was regulated

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predominantly by baroreceptor reflexes. The proposed mechanism of this CIVD response involves a sequence of neural reflexes elicited by cold pain, cold pressor response, baroreceptor reflex, and CIVD providing feedback inhibition of cold nociception. Differences in the pattern and regulation of CIVD may be related to the level of cold adaptation, and may influence the effectiveness of peripheral cryoprotection provided by CIVD.

ABSTRACT

The regulation and patterns of cold-induced vasodilation (CIVD) were identified by simultaneously monitoring circulatory and thermal responses during local cold exposure of a hindlimb in 22 cats anesthetized with chloralose. The different patterns of CIVD were categorized as hunting, sustained, combination of hunting and sustained, or no CIVD. The different regulatory mechanisms mediating CIVD were classified as baroreceptor mediated, active vasodilation, or redistribution of blood flow to skin. These cold unacclimatized cats produced primarily a hunting pattern of CIVD which was regulated predominantly by baroreceptor reflexes. The proposed mechanism of this CIVD response involves a sequence of neural reflexes elicited by cold pain, cold pressor response, baroreceptor reflex, and CIVD providing feedback inhibition of cold nociception. Differences in the pattern and regulation of CIVD may be related to the level of cold adaptation, and may influence the effectiveness of peripheral cryoprotection provided by CIVD.

KEY WORDS: Cold-induced vasodilation; cold exposure; baroreceptor reflex; active neurogenic vasodilation; local regulation; blood flow redistribution; anesthetized cat.

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INTRODUCTION

Sir Thomas Lewis (35) originally observed that a finger immersed in ice water is initially cooled, but is rewarmed after about five minutes. The rewarming of cold-exposed peripheral tissues was termed cold-induced vasodilation (CIVD). Subsequent studies have demonstrated an ubiquitous occurrence of CIVD among homeotherms (3,6,11,15,17,18,19,21,26,29,30,35,38,52). This suggests that CIVD is a fundamental physiological defensive response in peripheral tissues which is elicited by a cold stimulus and prevents cold injuries.

The regulation of CIVD is uncertain and contradictory. Proponents of the local regulation of CIVD have observed the occurrence of CIVD even after interruption of the peripheral sympathetic and somatic nerves (19,24,35,52). However, these denervations oftentimes attenuated or delayed subsequent CIVD responses suggesting that neural influences are one of several factors modulating CIVD responses. There has been no direct demonstrations of local mechanisms mediating CIVD. Proponents of the neurogenic regulation of CIVD were unable to demonstrate CIVD responses following interruption of the sympathetic nerves (38), peripheral nerves (30), and spinal cord (9,42). The marked hyperemia and peripheral warming occurring immediately after sympathectomy (5) suggests that inherent oscillations in efferent sympathetic vasoconstrictor tone may mediate CIVD responses.

These contradictory observations indicate that CIVD may actually be complexly regulated depending on the relative predominance of specific neural or local mechanisms. Since

previous investigations utilized primarily peripheral temperatures as an index of CIVD, little is known about concomitant circulatory changes associated with CIVD responses. The object of this study was to identify the different regulatory mechanisms affecting CIVD by simultaneously monitoring several circulatory and thermal responses during CIVD.

There are several physiological responses to cold which are mediated by the nervous system. These include cold sensation, cold pain, cold pressor response, CIVD and subsequent warmth or comfortable sensations. Previous studies dealt with each response separately, however it is probably of greater significance to view them collectively as a complex sequential physiological response to the common stimulus of cold. This study provides evidence of an interrelationship among these responses in the regulation of CIVD and also introduces the role of baroreceptors which had been previously overlooked.

METHODS

Experiments were performed on 22 cats anesthetized with α-chloralose (50 mg/kg iv), after induction with ketamine. In the hindlimb being studied for CIVD responses, mean femoral arterial blood flow was monitored with an electromagnetic flow probe and footpad temperature and heat loss were monitored with a thermocouple and heat flow disc taped to the metatarsal pad. In the contralateral hindlimb, the femoral artery and vein were cannulated to monitor mean arterial pressure and for fluid replacement with lactated Ringer's solution, respectively. ECG was monitored with standard limb leads and heart rate was derived with a cardiotach. A rectal thermistor was inserted for the continual monitoring of body temperature. Ambient temperature was monitored with a thermocouple. After insertion of an endotracheal tube, breathing was assisted with a positive-pressure respirator and ventilation was adjusted to maintain end-expiratory CO_2 between 4 and 5%.

All instruments were calibrated prior to each experiment. After anesthesia and surgical preparation of the cat, the physiological parameters simultaneously and continuously recorded were mean femoral arterial blood flow, footpad temperature, footpad heat loss, mean arterial pressure, heart rate, rectal temperature and ambient temperature. Transducer signals were simultaneously amplified and displayed on 4- and 8-channel chart recorders, recorded on magnetic tape, stored on-line with a computer, and displayed on a visual display terminal. Data stored by the computer were later retrieved to quantitate CIVD responses.

The experimental procedure involved recording data for five minutes with the hindlimb exposed to room air. The hindlimb was then inserted into a surgical glove and the entire gloved foot was immersed in a cold bath to the level of the heel. It was necessary to use a glove because electrical noise signals in heat flow and temperature were sometimes observed when in direct contact with the bath. The cooling bath was cooled with an external refrigerated circulating bath, which was adjusted in order to lower footpad temperature between 0° and 5°C. The foot was exposed to cold for 90 to 120 minutes. Skin temperature and heat flow declined exponentially until asymptotic levels were attained after a half hour. Consequently, the data obtained during the dynamic cooling period were removed in order to report CIVD data obtained after the foot had reached thermal equilibrium with the bath. Next, the cold bath was removed to re-expose the hindlimb to room air for 30 minutes. The foot was then exposed to cold for another 90 to 120 minutes in order to determine if the pattern of CIVD responses were consistent during repetitive cold exposures.

RESULTS

Indices of CIVD. By definition, CIVD is a rewarming of the skin during cold exposure (35). Consequently, skin temperature is the most common index of CIVD. In this study, femoral arterial blood flow, footpad temperature and footpad heat loss were generally satisfactory indices of CIVD (Fig. 1,2,4, and 6). Heat loss was the most sensitive index of CIVD since the relative amplitude of heat loss was much larger than that of skin temperature and blood flow during CIVD responses (Table 2). A hyperemia in the femoral artery was generally associated with footpad warming and heat loss. However, there was a delay of 1 to 15 minutes (8 $\pm$ 1 min) between an increase in femoral arterial blood flow and a warming of the footpad, which was related to the distance between these sites and that the entire length of the foot (10 to 14 cm) was cooled. Furthermore, it was uncertain what proportion of the femoral arterial blood flow was actually distributed to the footpad during CIVD responses. There was evidence that femoral arterial blood flow could be preferentially redistributed to the footpad in order to elicit a CIVD response (Fig. 5). Others report a good correlation between changes in blood flow, skin temperature and heat loss during CIVD responses (17,22,23). The simultaneous measurement of blood pressure was necessary in order to separate baroreceptor mediated CIVD responses from other regulatory categories.

Patterns of CIVD. Individual cats displayed different patterns of CIVD responses (Table 1). The different patterns of CIVD were categorized according to the duration of individual

CIVD responses after an initial period of vasoconstriction: (1) hunting CIVD, characterized by a momentary peripheral rewarming and heat dissipation which was generally associated with a hyperemia (Fig. 1,6); (2) sustained CIVD, characterized by a prolonged period of peripheral rewarming and heat dissipation which was generally associated with a hyperemia (Fig. 2); (3) combinations of hunting and sustained CIVD (Fig. 4); and (4) no CIVD, characterized by a lack of peripheral rewarming, increased heat dissipation, and hyperemia (Fig. 3). The majority of cats in this study displayed the hunting pattern of CIVD (Table 1). In general, these categories of CIVD patterns were similar to that of Schwinghamer and Adams (52). They proposed a potential fifth category of CIVD, characterized by a sustained warming occurring immediately upon cold exposure. This immediate CIVD upon cold exposure was observed in one cat (Fig. 6). However, the initial resistance of cold vasoconstriction by an immediate CIVD response does not fit Lewis' (35) definition of CIVD in which an initial cold vasoconstriction precedes subsequent CIVD responses.

The two cats which did not demonstrate CIVD responses deserve special attention (Fig. 3). They were both able to maintain femoral arterial blood flow between 5 and 6 ml/min, a level comparable to that of other cats which demonstrated CIVD responses (Table 2). Furthermore, their footpads were maintained at a temperature well above ambient and thus was associated with a sustained and high level of heat loss. This sustained pattern of peripheral warming during local cold exposure is the typical

pattern of CIVD observed in the cold adapted (6,15,18,26,34,40). Lewis (35) originally defined CIVD as periods of vasodilation which interrupted an initial vasoconstriction. This definition of CIVD is certainly applicable to the CIVD patterns in the cold unadapted, however it may need to be reassessed for CIVD patterns in the cold adapted which is typically a peripheral rewarming without an intense initial vasoconstriction. The lack of an initial period of vasoconstriction in these cats was the primary reason for categorizing their peripheral circulatory and thermal response as "no CIVD". Both cats were initially febrile, having rectal temperatures of 39.8° and 40.5°C, which may explain the sustained and elevated peripheral circulatory and thermal responses.

Characteristics of individual CIVD responses. There were considerable differences in the amplitude, duration, and frequency of CIVD responses within the same cat and among different cats (Table 2). This variability in CIVD responsiveness was attributed to variations in the duration and intensity of the regulatory mechanismss affecting it. Consequently, the lability of regulatory mechanisms considerably altered the characteristics of individual CIVD responses (Fig. 4,5 and 6). A marked variability in the amplitude and duration of CIVD responses has been observed by others (17,19,33,35,38,57). The inherent differences in CIVD responsiveness within the same individual and among different individuals within the same species make an interspecies comparison of CIVD responsiveness difficult. Despite

quantitative differences in CIVD responsiveness, the characteristic pattern of CIVD was generally repeated within the same cat (Table 1).

CIVD patterns during two cold exposures. Nineteen cats were exposed to cold twice with an intervening period of re-exposure to room air for a half hour. The recurrence of the same pattern of CIVD during both cold exposures was observed in 13 cats (68%); different patterns of CIVD during each cold exposure were observed in 6 cats (32%).

Regulation of CIVD. The simultaneous measurements of several circulatory and thermal responses has enabled the identification of various regulatory mechanism influencing individual CIVD responses. The different regulatory mechanisms were categoried according to whether periods of peripheral rewarming and heat dissipation were also associated with concomitant pressor or hyperemia responses (Table 3). Both hunting and sustained patterns of CIVD could be regulated by baroreceptor reflexes or active vasodilation. There was evidence of only one regulatory mechanism mediating all CIVD responses in 14 cats (Fig. 1,2,5 and 6); whereas a combination of both active and baroreceptor mediation of CIVD responses was observed in 6 cats (Fig. 4). The most common regulatory mechanism was the baroreceptor reflex mediation of 77% of the individual CIVDs in 73% of these cold unacclimatized cats. The most unusual regulatory mechanism was a redistribution of blood flow to skin influencing 5 hunting CIVDs in only one cat.

Baroreceptor mediated CIVDs were characterized by a

concomitant pressor response, peripheral hyperemia, and footpad warming and heat dissipation (Fig. 1 and 6). The peripheral circulatory and thermal responses were attributed to a reflex inhibition of descending sympathetic vasoconstrictor tone by baroreceptors responding to a pressor response. It is also possible that an increase in perfusion pressure during pressor responses resulted in the CIVD responses, however the decreased vascular resistance (Fig. 1 and 6) associated with CIVD responses indicates a baroreceptor mediated reflex vasodilation instead. It is important to note that mean arterial pressure became increasingly labile during local cold exposure, thus providing the potential for the elicitation of baroreceptor reflex effects on peripheral circulation.

The regulatory category termed "active vasodilation" included all other CIVD responses which were associated with a peripheral hyperemia, rewarming, and increased heat dissipation; but were not associated with concomitant pressor response (Fig. 4). It was uncertain if active vasodilation was elicited by neural or local mechanisms.

A third regulatory mechanism mediating individual CIVD responses was termed "redistribution of blood flow to skin." This regulatory category was characterized by an independent rewarming and increased heat loss from the footpad, which was not associated with a femoral arterial hyperemia (Fig. 5). The cutaneous warming could occur only if the peripheral blood flow was selectively shunted to the skin rather than muscles. The regulation of CIVD by a redistribution of peripheral blood flow

to skin was unusual, occurring in only one cat. There was evidence that the selective shunting of blood flow to skin was mediated by baroreceptors. It is uncertain what proportions of the femoral arterial hyperemia observed during baroreceptor mediated and active vasodilation were separately distributed through the vasculature in skin and skeletal muscle.

Effects of local cold exposure on body temperature and heart rate. The cats were unable to maintain normothermia during local cold exposure. A progressive hyothermia was observed during both periods of local cold exposure regardless of the initial level of body temperature (Fig. 1,2,3,4,5, and 6). However, rectal temperature was unchanged during the intervening half hour in which the hindlimb was re-exposed to room air. There was evidence that excessive and prolonged CIVD responses exacerbate the rate of hypothermia (Fig. 2 and 6).

Generally a progressive bradycardia was associated with the proressive hypothermia during local cold exposure (Fig. 1,2,3,4 and 5). Heart rate was relatively unchanged during the intervening half hour of hindlimb re-exposure to room air. In some cats, momentary periods of tachycardia were associated with pressor responses and momentary periods of bradycardia were associated with depressor responses (Fig. 1,2, and 5), suggesting a uniform sympathetic outflow affecting both responses. Whereas an inverse relationship between changes in heart rate and blood pressure (Fig. 6) suggests the involvement of baroreceptor reflex effects on heart rate. It should be noted that momentary periods of tachycardia and pressor responses were oftentimes associated

with a concomitant peripheral vasodilation and hyperemia (Fig. 1 and 5) suggesting a differential sympathetic outflow simultaneously influencing different responses.

DISCUSSION

Local cold exposure produces an initial peripheral vasoconstriction and a reduction in peripheral blood flow mediated by both a direct vascular constrictor effect of cold and a neurogenic reflex vasoconstriction (19,38,45). Immediately after local cold exposure, there was a reduction in peripheral blood flow, a cooling of the footpad, and a diminution of footpad heat loss. This redistribution of blood away from the periphery conserves heat within the body core. The existence of peripheral vasoconstriction is also a fundamental prerequisite for subsequent vasodilatory responses. There is an apparently limited tolerance of peripheral tissues to cold and ischemia, consequently periods of hyperemia and warming are necessary to prevent cold injuries. Thus CIVD may be viewed as a vascular escape mechanism which allows peripheral rewarming during continued cold exposure.

CIVD responses were observed in 91% of these 22 cold unacclimatized cats, of which 86% displayed the hunting pattern of CIVD. Similar observations were made on 102 cats by Schwinghamer and Adams (52). The hunting pattern of CIVD is observed primarily in the cold unadapted (11,17,19,22,23,24,28,29,35,36,52,57). Periods of sustained CIVD was observed 23% of these cats. The sustained pattern of CIVD is observed primarily in the cold adapted (6,15,18,26,34,40).

The marked increase in peripheral blood flow during CIVD passes through cutaneous arteriovenous anastomoses (16,21). Bilateral lumbar sympathectomy produces a hyperemia in the

nuclei. The resulting diminution in efferent sympathetic constrictor tone allows the passive vasodilation of cutaneous arteriovenous anasotomoses, i.e. CIVD. The cutaneous hyperemia povides feedback inhibition of cold nociceptors since the cold nociceptors are inactivated by tissue warming. Without afferent nociceptive activity, all subsequent signals eliciting CIVD responses would be terminated and the lack of circulatory warmth allows cooling of peripheral tissues. Meanwhile the skin is momentarily warmed to the threshold required for the activation of cold thermoreceptors. Cold sensory afferents ascend to the preoptic and anterior hypothalamic thermoregulatory nuclei which reflexly increase descending sympathetic vasoconstrictor tone. The resulting diminution in peripheral blood flow would allow a cooling of peripheral tissues until the threshold for the activation of cold nociceptors is again attained, which initiates another CIVD response.

There is evidence supporting various facets of the baroreceptor mediated regulation of CIVD hypothesis. It is probably of great significance to note an overlap in the threshold for the elicitation of CIVD responses, cold pain and cold pressor responses. Lewis (35) determined that the best ambient temperature for inducing CIVD is between 0° and 7°C, with less frequent CIVDs in temperatures up to 18°C, and no CIVDs at warmer temperatures. Simlarly, there is no sensation of pain or elevation of blood pressure during hand immersion in water warmer than 18°C, and the intensity of cold pain and amplitude of cold pressor responses were directly related to each other and to

cutaneous arteriovenous anastomoses of dog hindlimbs and peripheral warming (14). This study provides supporting evidence that the tonic cold induced sympathetic constrictor influence on cutaneous arteriovenous anastomoses is inhibited by the baroreceptor reflex, resulting in CIVD. The marked hyperemia through arteriovenous anastomoses implies that the primary function of CIVD is to rewarm peripheral tissues rather than the removal of metabolites and replenishment of oxygen and other nutrients to ischemic tisues since there is no evidence of an increase in microcirculation during CIVD.

The results of this study provide evidence that CIVD responses may be regulated by different mechanisms. Baroreceptor mediated regulation of CIVD predominated in the majority of CIVD responses. The remainder of CIVD responses were regulated by active vasodilation or a redistribution of peripheral blood flow to the skin.

The proposed mechanism of baroreceptor mediated regulation of CIVD is shown in Figure 7. Exposure to cold sufficient to activate cold nociceptors initiates a complex sequential series of responses. Afferent nociceptive information ascends to the somatosensory cortex where cold pain is perceived. Afferent nociceptive information also ascend to the cardiovascular nuclei in the brainstem where a somatosympathetic reflex inducing cold pressor responses is elicited. Next baroreceptors responding to the pressor response reflexly inhibit the large sympathetic vasoconstrictor tone, which was originally induced by cold exposure and which descend from the brainstem cardiovascular

increasing coldness(55,56). The sensation of cold pain is diminished during CIVD (23,35,56). The sensation of cold pain varies among individuals (4), diminishes with repetitive cold exposures (3,15,20,57) and is less evident in the cold adapted (15,18,34,40). However, the cold pressor response is observed even after a diminution in cold pain (4,20). This suggests a divergence in the ascending cold nociceptive pathway in which the sensory pathway may be centrally inhibited to reduce the sensation of cold pain yet the somosympathetic pathway producing cold pressor responses is unperturbed. The activation of noxious cutaneous afferents can reflexly produce a sympathetically mediated pressor response (51). A similar somatosympathetic reflex activated by cold nociceptors may elicit the cold pressor response. Pressor responses were associated with CIVD responses in the ox ear (29). Baroreceptors responding to pressor responses during bilateral common carotid artery occlusions reflexly mediate a peripheral hyperemia and warming during local cold exposure (43). CIVD responses are mediated primarily by variations in efferent sympathetic vasoconstrictor tone (38). Sympathectomy enhances the blood flow through arteriovenous anastomoses resulting in cutaneous warming (14). During CIVD, the total blood flow passes through arteriovenous anastomoses (16).

The regulatory categories of "active vasodilation" and "redistribution of blood flow to skin" may be mediated by several potential mechanisms. A diminution in central sympathetic vasoconstrictor outflow, not mediated by baroreflex inhibition,

may allow a passive hyperemia to the entire hindlimb or specifically to the footpad. Another mechanism would be the active neurogenic vasodilation of specific cutaneous vasculature. A third possibility is vasodilation mediated by local mechanisms, of which there are several subcategories. The specific mechanism mediating these regulatory categories could not be identified in this study.

There are at least two neural pathways mediating active peripheral vasodilation. A sympathetic cholinergic vasodilator pathway mediates the vasodilation of vasculature primarily in skeletal muscle (11,53). The arteriovenous anastomoses in human skin also possess cholinergic innervation (27). A sympathetically mediated active vasodilation of human cutaneous vasculature enhances heat loss during exposure to heat (50). Whether sympathetic cholinergic vasodilation of vasculature in the skin of mammals occurs during cold exposure is uncertain. There is evidence that CIVD responses in the skin of the giant fulmar are mediated by the activation of sympathetic cholinergic mechanisms during cold exposure (30). A noncholinergic sympathetic cutaneous vasodilation has been observed in dogs (2,49). This active cutaneous neurogenic vasodilatory pathway may actually be mediated by dopaminergic dilatation of arteriovenous anastomoses in the footpad of dogs (7,8). A similar peripheral hyperemia to intravenously administered dopamine was observed in the cold exposed hindimb of cats in this laboratory (Ohata, unpublished observations). However the dopamine induced hyperemia was due to its effect on α-adrenergic

receptors, not dopamine receptors, since the response persisted after pretreatment of the cats with the dopamine receptor blocker ergonovine but was blocked after pretreatment with the α-adrenergic blocker phentolamine. The species differences in sympathetic cholinergic and dopaminergic vasodilatory mechanisms, and whether they are functioned during cold exposure, considerably complicates their involvement in the mediation of CIVD. Furthermore the active neurogenic vasodilatory pattern of CIVD may be mediated by an as yet unidentified neural pathway involving prostaglandins, purines, histamine,or neuropeptides.

It is possible that several local mechanisms may mediate CIVD independently of neural influences or modulate neural influences to produce CIVD responses. A momentary autoregulatory escape may produce a CIVD response and restore blood flow to ischemic tissues. However, there is no evidence of local anoxia, hypercapnia or acidosis mediating CIVD responses (11). Perhaps a reversal of the Bayliss response in which a decreased perfusion pressure causing myogenic relaxation may induce a CIVD response, but there is no supporting evidence. Cold below 9°C blocks neural conduction (10); however, unmyeliated sympathetic C fibers are not blocked at 0°C (37). This suggests that CIVD responses are not induced by the direct blockage of efferent sympathetic vasoconstrictor nerves by cold. Perhaps the most plausible explanation for the local regulation of CIVD is the observation that cold depresses the contractility of vascular smooth muscle to norepinephrine (19,31,39,41). This direct suppression of vascular contractility, despite continued efferent sympathetic

vasoconstrictor activity, may induce a CIVD response until the vasculature is rewarmed to restore its contractile response to norepinephrine. The possibility of a sensory axon reflex release of histamine mediating CIVD responses (35) was subsequently disproved when pretreatment with antihistamines failed to block CIVD responses (19,52,54). There is evidence of an increase in the formation of the vasodilator bradykinin from kininogen during CIVD, and a reduction in local bradykinin during cold vasoconstriction (12). Other unidentified vasoactive humoral agents may also affect CIVD responses.

The highly selective and nonuniform activation or inactivation of specific autonomic efferent pathways is responsible for a diversity of cardiovascular responses (2). It is possible that specific neurogenic vasodilatory mechanisms may be involved in the redistribution of blood flow to skin. Stimulation of peripheral nerves produces a nonhomogeneous redistribution of dog hindlimb blood flow to specific vascular beds (1,13).

The physiological significance of CIVD is teleologically related to the prevention of cold injuries in peripheral tissues (35). However, the incidence of cold injuries depends on the duration and amplitude of CIVD responses and the duration and severity of the cold exposure. It is paradoxical that tissues having the best CIVD responses, i.e. fingers, toes, and ears (35) are also more prone to cold injuries. This investigation proposes that cold nociception is important in inducing CIVD responses. Consequently numbness, the cold blockage of

peripheral sensations, interrupts the sequelae leading to CIVD responses and may be the first prognosis of impending cold injuries.

Cold adaptation appears to have the most profound effect on the pattern of CIVD responses. Differences in the pattern and regulation of CIVD between the cold acclimatized and unacclimatized may be a primary determining factor on the effectiveness of cryoprotection provided by CIVD.

The hunting pattern of CIVD occurs primarily in the cold unacclimatized (Present study; 11,17,19,22,23,24,28,29,35,36,52, 57). The oscillatory nature of hunting CIVD in the cold unacclimatized, in which periods of over-compensation with a massive peripheral rewarming alternate with periods of under-compensation with an intense vasoconsriction, indicates a lack of refined steady-state regulation of responses to a maintained cold stress. These hunting responses were more closely related to a labile systemic pressure in which baroreceptor reflexes elicited unstable peripheral vascular responses. The cold pressor response is greater in the cold unacclimatized than in the cold acclimatized (33,34,55). The pain oftentimes observed in the cold unacclimatized (4) occurs during periods of intense vasoconstriction during which the periphery is cooled to the level of activation of nociceptors. The validity of cryoprotection by hunting CIVD responses is uncertain since laboratory tests are too short for the full development of cold injuries. There is evidence that prolonged cold exposure may not enhance CIVD responsiveness (25,36).

Peripheral tissues may become more susceptible to cold injuries during the vasoconstrictive state in the cold unacclimatized. Perhaps for this reason there is a higher incidence of cold injuries among the cold unacclimatized during prolonged exposure to cold under natural conditions, a group in which the hunting pattern of CIVD is prevalent. The highest incidence of cold injuries is expected to occur in those individuals not producing any CIVD responses at all (28).

The sustained pattern of CIVD, in which there is a continuous warming of the extremities during cold exposure, is observed in the cold acclimatized (6,15,18,26,34,40). This stable peripheral circulatory response suggests the existence of a finely and effective regulation of CIVD in direct proportion to the level of cold stress in the cold adapted. The sustained CIVD provides continuous peripheral cryoprotection in the cold adapted in contrast to the transient cryoprotection of hunting CIVD in the cold unadapted. During cold acclimatization, there appears to be a transition in the pattern and regulation of CIVD from the baroreceptor mediated hunting CIVD to the sustained CIVD possibly mediated by active vasodilation. The CIVD pattern of the cold adapted does not have the initial intense vasoconsriction and is primarily characterized by maintained peripheral warmth during local cold exposure (6,15,18,26,34,40). Their diminished sensation of cold pain (18,34,40) may be related to the maintenance of peripheral warmth below the threshold for activation of cold nociceptors. In Eskimos, the cold pressor response is diminished (33) and the incidence of hypertension is

rare (48). This suggests an enhanced baroreceptor sensitivity among Eskimos which may exacerbate CIVD responses and maintain normotension. These adaptations may be the result of natural selection since there is a noticeable lack of reported cold injuries or Raynaud's disease among the cold adapted. The enhanced CIVD response is a functional adaptation instead of morphological since there are no reports of increased vascularization in the skin of the cold adapted. The enhanced CIVD is presumably restricted to specific uninsulated sites since the remainder of the body surface is insulated against heat loss. In contrast, the ama, whose entire body surface is exposed to cold, have a diminished CIVD response which restricts the rate of body cooling (44). Either repetitive or continuous cold exposure appears to enhance the CIVD responses of the previously cold unadapted. The CIVD pattern is changed with an earlier initiation, more rapid rewarming, higher peak temperature, and either an elevated, sustained or more labile temperatures (3,15,18,52,57) and associated with a diminished sensation of cold pain (3,15,20,57) and a diminished cold pressor response (33). This suggests that the cold unadapted may develop CIVD responses similar to that of the cold adapted during cold acclimation.

A progressive hypothermia was observed only during local cold exposure. Normothermia was maintained only when the hindlimb was not exposed to cold suggesting a minimal anesthetic depession of thermoregulatory capabilities. Hypothermia is expected to elicit themoregulatory heat conservation mechanisms which would inhibit

CIVD responses. Yet the occurrence of CIVD responses, even during hypothermia, suggests that the peripheral mechanism protecting against cold injuries overrides the simultaneous thermoregulatory drive to reduce excessive heat loss during cold exposure. In some cats, the rate of hypothermia was momentarily exacerbated by CIVD responses. CIVD also occurs in moderately (35°C) and severely (28-25°C) hypothermic dogs (11). However, others (22) report that the amplitude of CIVD responses is enhanced by body heating and diminished by body cooling. It is obvious that the continued loss of heat, especially during CIVD, was detrimental to the maintenance of normothermia in anesthetized cats. Under natural conditions, CIVD is expected to occur in associaion with physical activity. Increased metabolic heat production would then compensate for the excessive losses of heat via CIVD, and normothermia would be maintained.

The hypothermia may have produced secondary cardiovascular effects. Progressive hypothermia is associated with a progressive depression of heart rate, stroke volume, cardiac output and arterial pressure, and hemoconcentration with a resultant decrease in peripheral blood flow (46,47). In this study, only a progressive bradycardia could be correlated with the progressive hypothermia. Furthermore, carotid baroceptor reflexes persist in hypothermia to 24°C (32). There was evidence of baroreceptor mediated CIVD responses in these hypothermic cats.

It is evident that CIVD is a complex response in which a multiplicity of factors affects the overall pattern of CIVD. The

net CIVD response in each individual reflects the relative predominance of several potential regulatory mechanisms. The cold unacclimatized cat produces primarily a hunting pattern of CIVD which is regulated by baroreceptor reflexes.

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Figure 1. Pattern of hunting CIVD, characterized by momentary increases in skin temperature, heat flow and blood flow. Pressor responses and decreased vascular resistances associated with each hunting CIVD provide evidence of baroreceptor reflex regulation of CIVD.

Figure 2. Pattern of sustained CIVD, characterized by maintained increases in skin temperature(S), heat flow, and blood flow during local cold exposure (A). The elevated level of blood pressure associated with the sustained hyperemia provides evidence of baroreceptor mediation of CIVD.

Figure 3. Pattern of no CIVD, characterized by a lack of peripheral hyperemia, rewarming, and heat dissipation.

Figure 4. Pattern of a combination of sustained (40 to 75 minutes) and hunting (75 to 90 minutes) CIVD, each of which were associated with different levels of blood flow, skin temperature(S), and heat flow during local cold exposure (A). The hunting CIVD was not associated with a pressor response, and the regulatory mechanism was categorized as an active vasodilation.

Figure 5. CIVD responses (40 to 90 minutes) which were regulated by a redistribution of blood flow to skin(S). This regulatory mechanism was characterized by a warming and increased heat dissipation of the footpad which was not accompanied by a peripheral hyperemia even though blood pressure became elevated and increasingly labile.

Figure 6. Effects of different levels of CIVD on body temperature. A profound initial CIVD (0 to 45 minutes),

characterized by an intense vasodilation, marked hyperemia, extremely warm skin, and massive heat dissipation, resulted in a rapid hypothermia. This rapid body cooling was deterred by a three-fold increase in peripheral vasoconstriction (45 to 90 minutes), which restricted peripheral blood flow and reduced skin temperature and heat loss, although there were interruptions by small amplitude hunting CIVDs. All CIVD responses were mediated by baroreceptor reflexes.

Figure 7. Hypothesis of the mechanisms involved in baroreceptor regulation of CIVD.

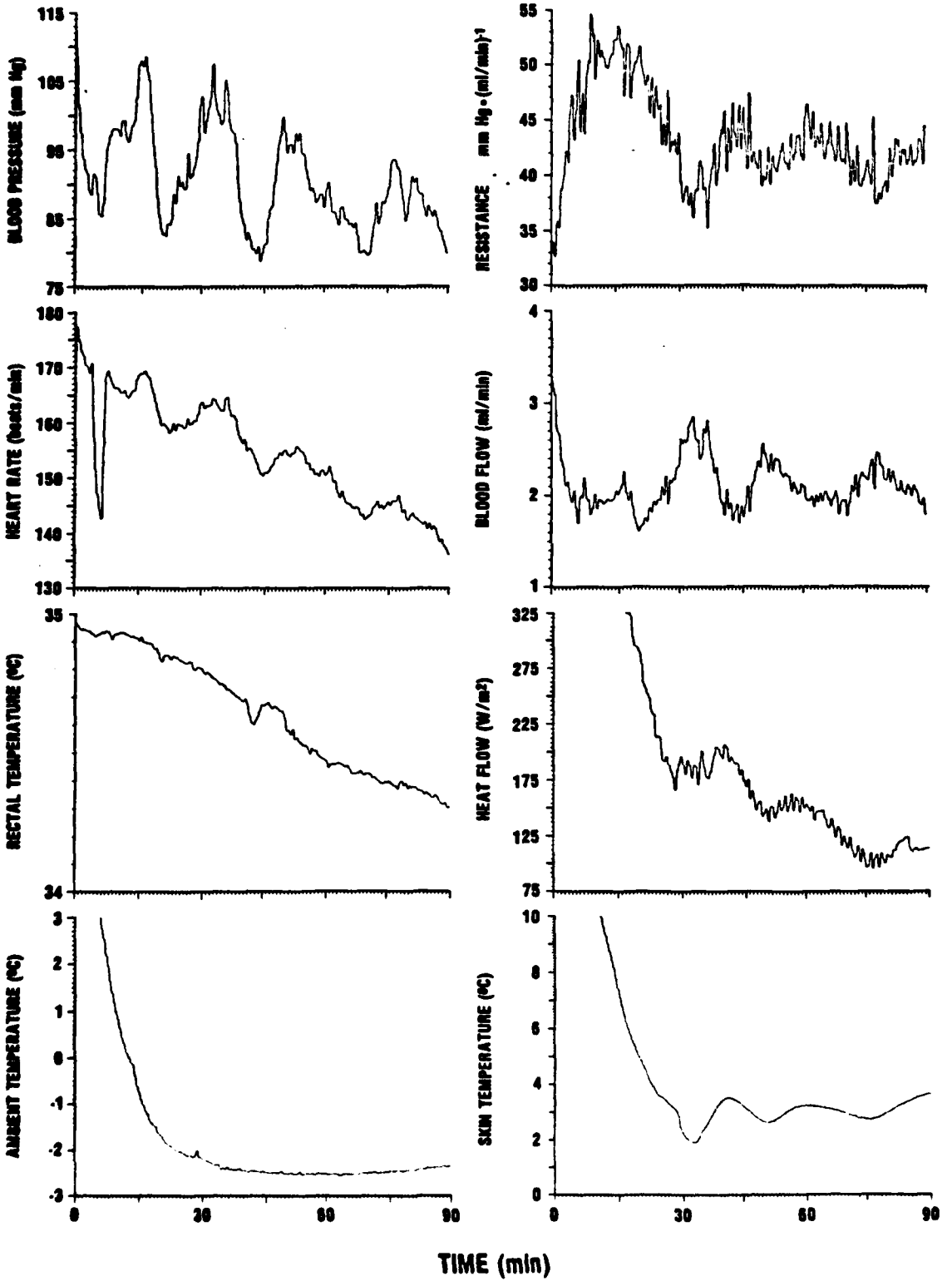
The views, opinions, and/or findings contained in this report are those of the author and should not be construed as an official Department of the Army position, policy, or decision, unless so designated by other official documentation.

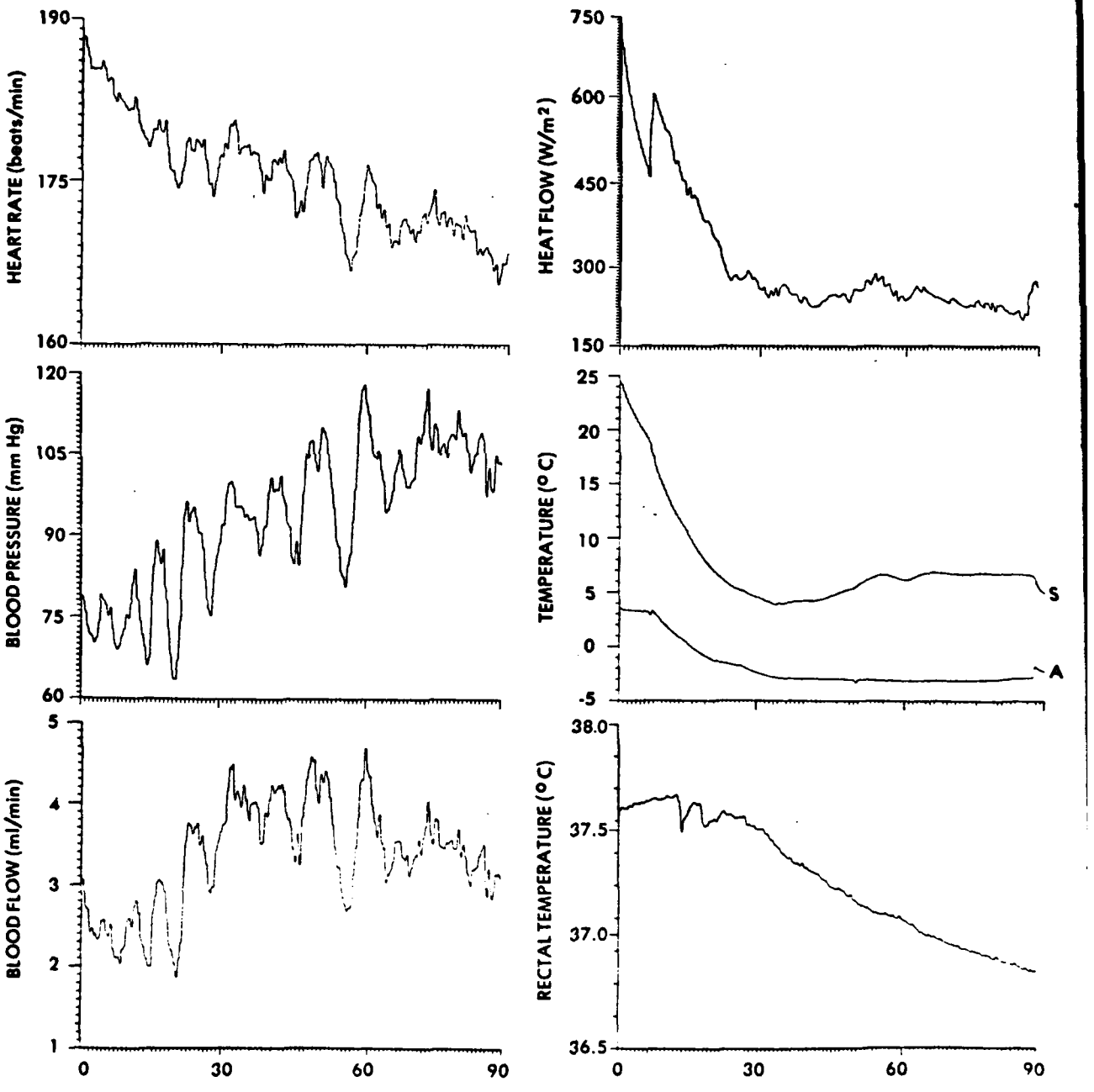
The conduct of the research described in this report adhered to the "Guide for Laboratory Animal Facilities and Care," as promulgated by the Committee on the Guide for Laboratory Animal Facilities and Care of the Institute of Laboratory Animal Resources, National Academy of Sciences, National Research Council.

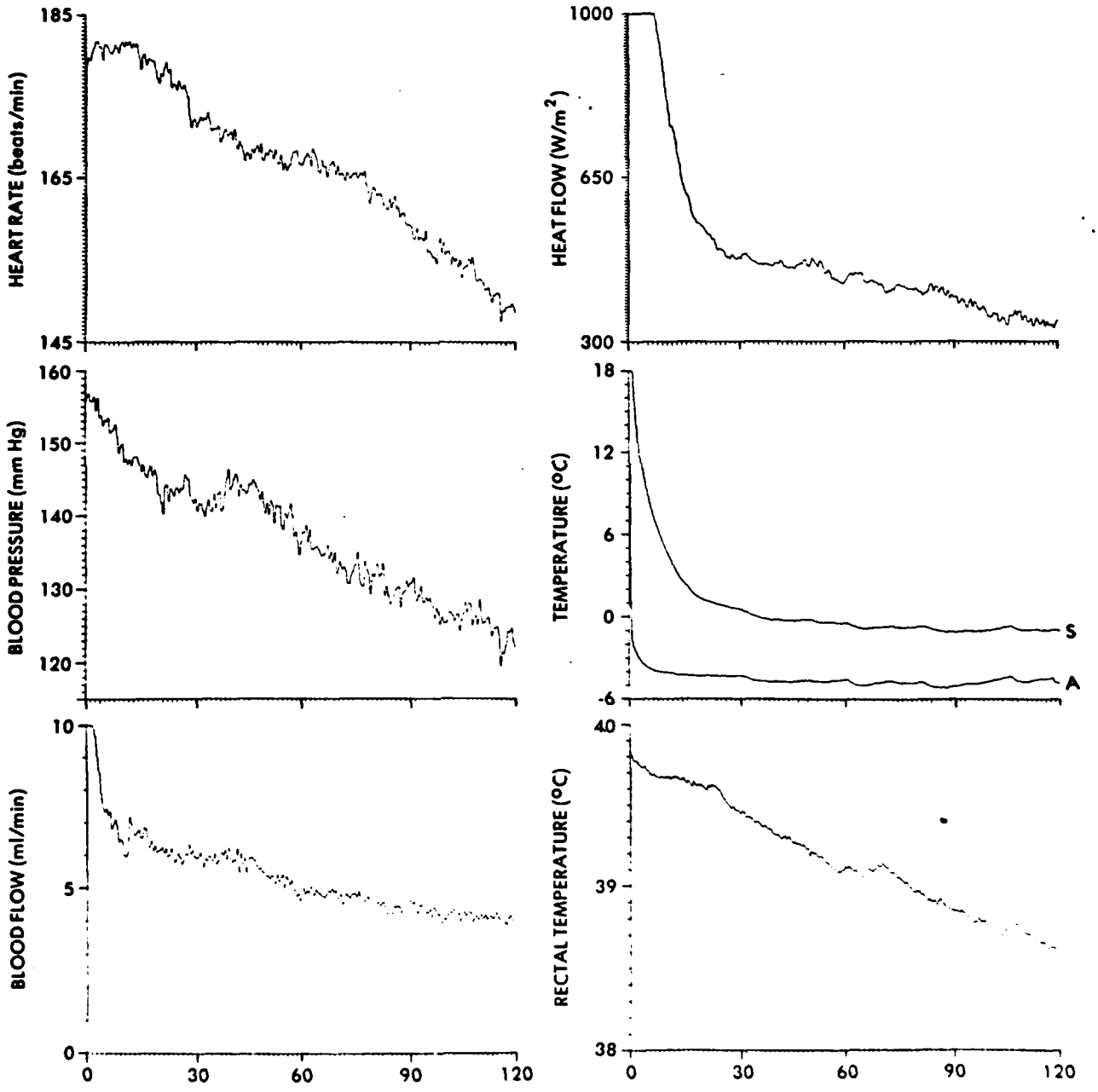
TABLE 1. Patterns of CIVD responses in the hindlimb of anesthetized cats from this study and that of Schwinghamer and Adams (52)

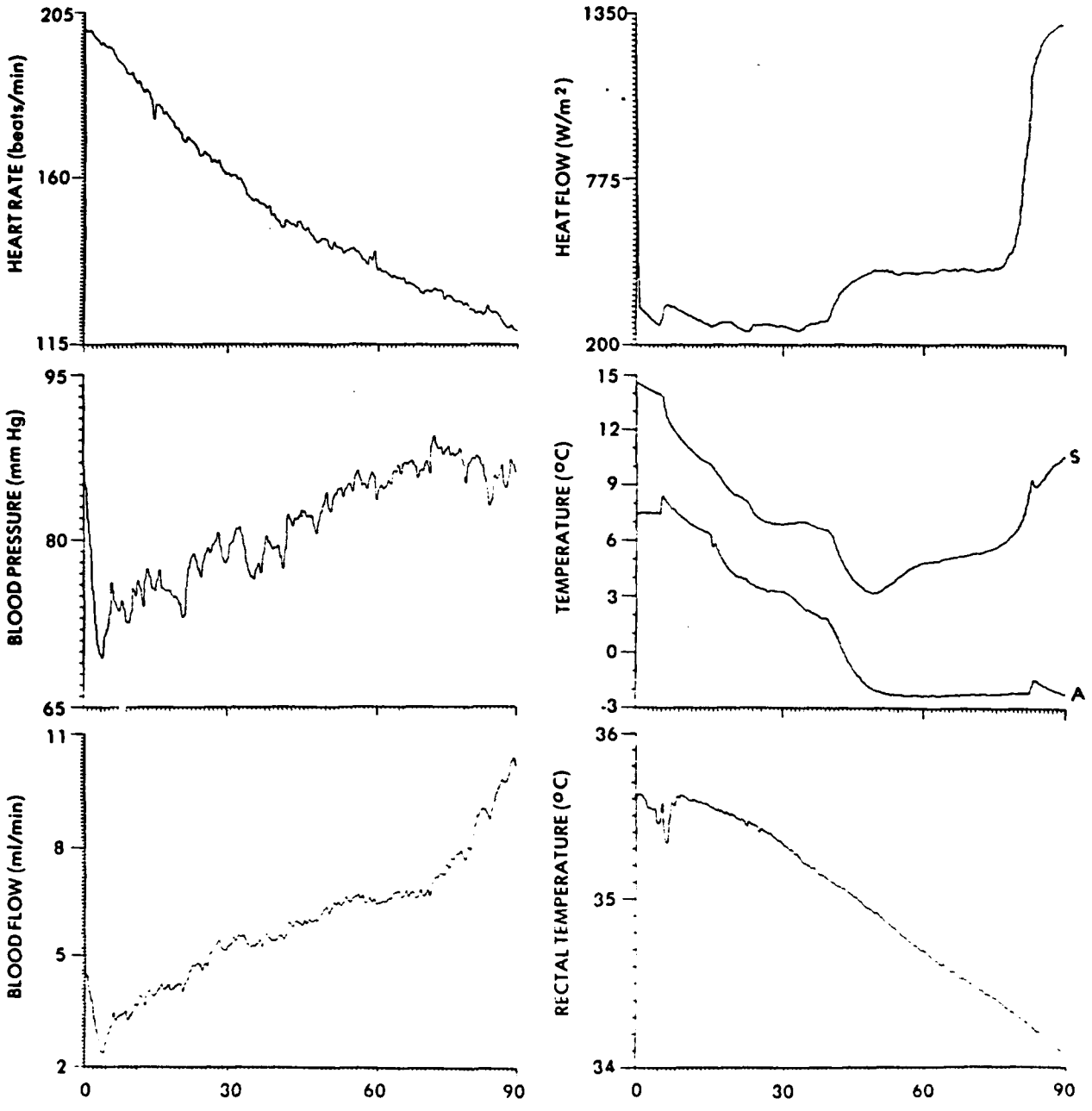
Response Type	This Study n	This Study % Total	Schwinghammer & Adams % Total*
Hunting	15	68%	76%
Sustained	1	5%	14.6%
Hunting & Sustained	4	18%	None reported
No CIVD	2	9%	9.4%

*n = 102 cats


BLOOD PRESSURE (mm Hg)
115
105
95
85
75
RESISTANCE mm Hg • (ml/min)⁻¹
55
50
45
40
35
30
HEART RATE (beats/min)
180
170
160
150
140
130
BLOOD FLOW (ml/min)
4
3
2
1
RECTAL TEMPERATURE (°C)
35
34
HEAT FLOW (W/m²)
325
275
225
175
125
75
AMBIENT TEMPERATURE (°C)
3
2
1
0
-1
-2
-3
SKIN TEMPERATURE (°C)
10
8
6
4
2
0
0
30
60
90
TIME (min)


HEART RATE (beats/min)
190
175
160
HEAT FLOW (W/m²)
750
600
450
300
150
BLOOD PRESSURE (mm Hg)
120
105
90
75
60
TEMPERATURE (°C)
25
20
15
10
5
0
-5
S
A
BLOOD FLOW (ml/min)
5
4
3
2
1
RECTAL TEMPERATURE (°C)
38.0
37.5
37.0
36.5
0
30
60
90
TIME (min)


HEART RATE (beats/min)
185
165
145
HEAT FLOW (W/m²)
1000
650
300
BLOOD PRESSURE (mm Hg)
160
150
140
130
120
TEMPERATURE (°C)
18
12
6
0
-6
S
A
BLOOD FLOW (ml/min)
10
5
0
RECTAL TEMPERATURE (°C)
40
39
38
0
30
60
90
120
TIME (min)


HEART RATE (beats/min)
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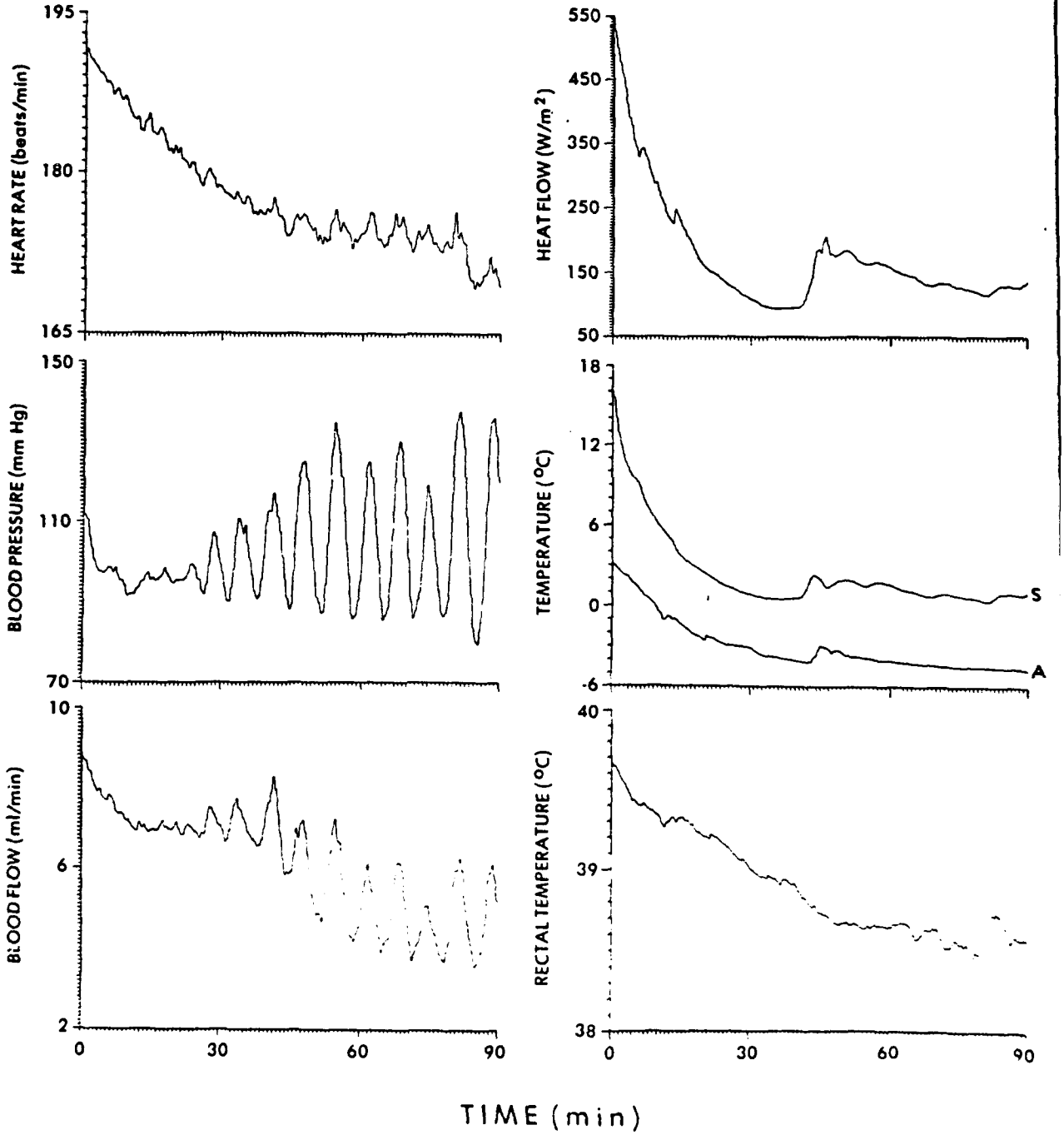
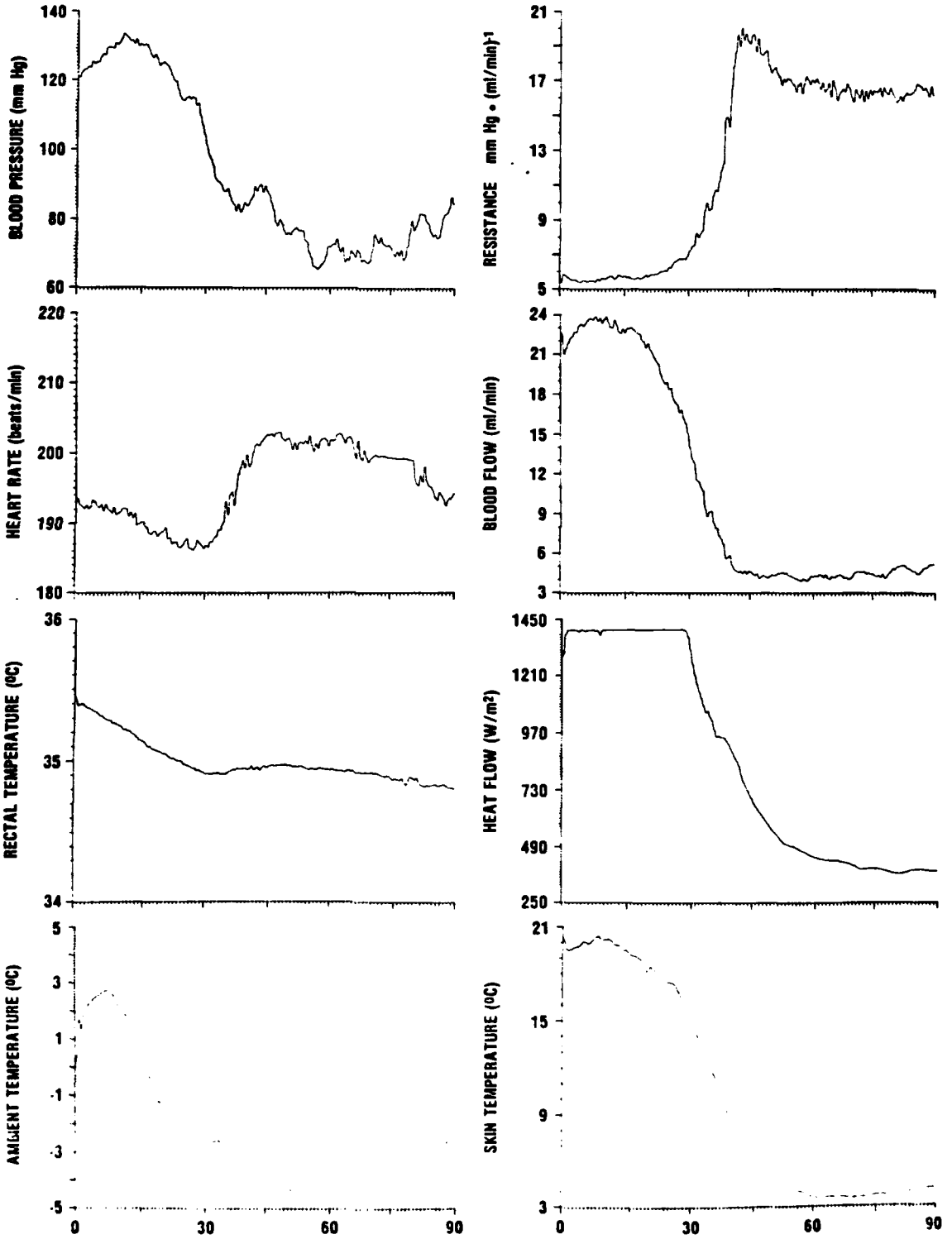
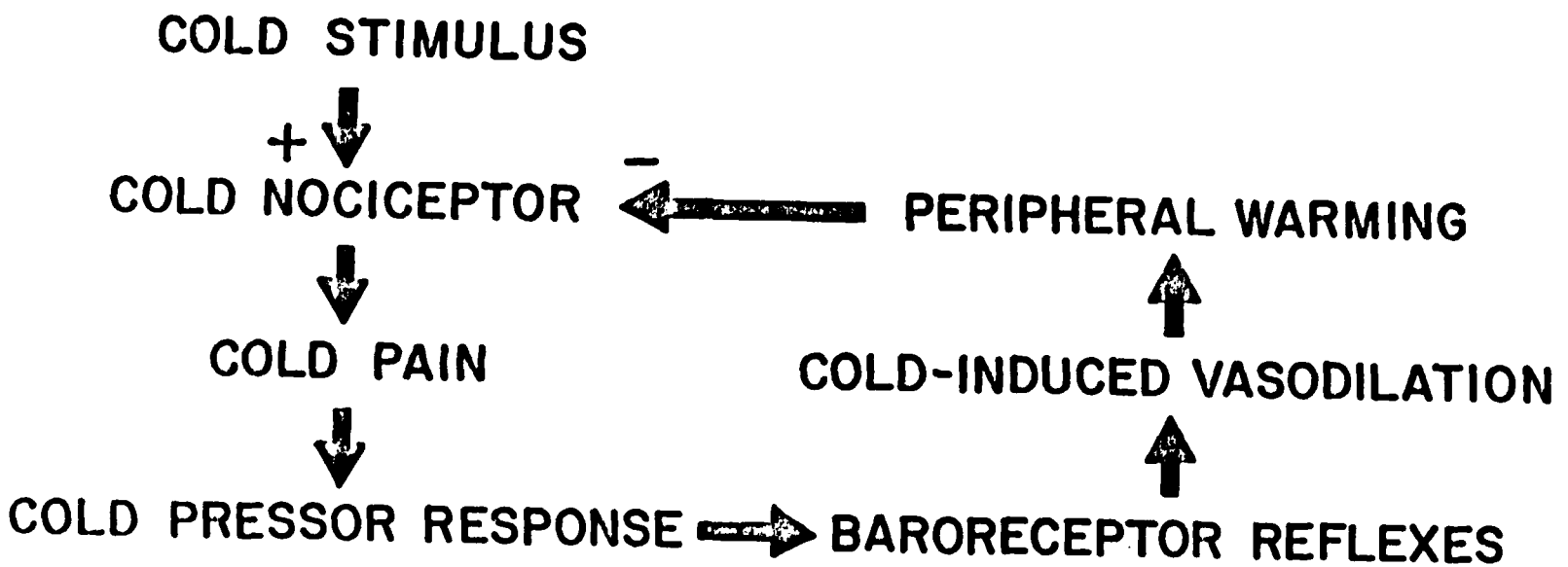
160
115
HEAT FLOW (W/m²)
1350
775
200
BLOOD PRESSURE (mm Hg)
95
80
65
TEMPERATURE (°C)
15
12
9
6
3
0
-3
S
A
BLOOD FLOW (ml/min)
11
8
5
2
RECTAL TEMPERATURE (°C)
36
35
34
0
30
60
90
TIME (min)


HEART RATE (beats/min)
195
180
165
HEAT FLOW (W/m²)
550
450
350
250
150
50
BLOOD PRESSURE (mm Hg)
150
110
70
TEMPERATURE (°C)
18
12
6
0
-6
S
A
BLOOD FLOW (ml/min)
10
6
2
RECTAL TEMPERATURE (°C)
40
39
38
0
30
60
90
TIME (min)


BLOOD PRESSURE (mm Hg)
140
120
100
80
60
RESISTANCE mm Hg • (ml/min)-1
21
17
13
9
5
HEART RATE (beats/min)
220
210
200
190
180
BLOOD FLOW (ml/min)
24
21
18
15
12
9
6
3
RECTAL TEMPERATURE (°C)
36
35
34
HEAT FLOW (W/m²)
1450
1210
970
730
490
250
AMBIENT TEMPERATURE (°C)
5
3
1
-1
-3
-5
SKIN TEMPERATURE (°C)
21
15
9
3
0
30
60
90
TIME (min)


COLD STIMULUS
+
COLD NOCICEPTOR
−
PERIPHERAL WARMING
COLD PAIN
COLD-INDUCED VASODILATION
COLD PRESSOR RESPONSE
BARORECEPTOR REFLEXES

9-84

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